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Maternal Phthalate and Bisphenol Urine Concentrations during Pregnancy and Early Markers of Arterial Health in Children

Sophia M. Blaauwendraad,[1,2] Romy Gaillard,[1,2] Susana Santos,[1,2] Chalana M. Sol,[1,2] Kurunthachalam Kannan,[3,4] Leonardo Trasande,[3,4,5,6,7] and Vincent W.V. Jaddoe[1,2]**

[1]The Generation R Study Group, Erasmus Medical Center (MC), University Medical Center, Rotterdam, Netherlands
[2]Department of Pediatrics, Erasmus MC, University Medical Center, Rotterdam, Netherlands
[3]Department of Pediatrics, New York University School of Medicine, New York, New York, USA
[4]Department of Environmental Medicine, New York University School of Medicine, New York, New York, USA
[5]Department of Population Health, New York University School of Medicine, New York, New York, USA
[6]New York University Wagner School of Public Service, New York University, New York, New York, USA
[7]New York University College of Global Public Health, New York University, New York, New York, USA

Background: Fetal exposure to endocrine-disrupting chemicals such as phthalates and bisphenols might lead to fetal cardiovascular developmental adaptations and predispose individuals to cardiovascular disease in later life.

Objectives: We examined the associations of maternal urinary bisphenol and phthalate concentrations in pregnancy with offspring carotid intima-media thickness and distensibility at the age of 10 y.

Methods: In a population-based, prospective cohort study of 935 mother–child pairs, we measured maternal urinary phthalate and bisphenol concentrations at each trimester. Later, we measured child carotid intima-media thickness and distensibility in the children at age 10 y using ultrasound.

Results: Maternal urinary average or trimester-specific phthalate concentrations were not associated with child carotid intima-media thickness at age 10 y. Higher maternal average concentrations of total bisphenol, especially bisphenol A, were associated with a lower carotid intima-media thickness [differences −0.15 standard deviation score and 95% confidence interval (CI): −0.24, −0.09 and −0.13 (95% CI: −0.22, −0.04) per interquartile range (IQR) increase in maternal urinary total bisphenol and bisphenol A concentration]. Trimester-specific analysis showed that higher maternal third-trimester total bisphenol and bisphenol A concentrations were associated with lower child carotid intima-media thickness [differences −0.13 (95% CI: −0.22, −0.04) and −0.13 (95% CI: −0.22, −0.05) per IQR increase in maternal urinary bisphenol concentration]. Maternal urinary bisphenol or phthalate concentrations were not associated with child carotid distensibility.

DISCUSSION: In this large prospective cohort, higher maternal urinary bisphenols concentrations were associated with smaller childhood carotid intima-media thickness. Further studies are needed to replicate this association and to identify potential underlying mechanisms. https://doi.org/10.1289/EHP10293

Introduction

Endocrine-disrupting chemicals (EDCs) such as bisphenols and phthalates are widely used in the production of common consumer products, including plastic bottles, thermal papers, and food-can coatings.[1–4] Bisphenols and phthalates pass the placental barrier leading to direct fetal exposure.[5] It has been hypothesized that fetal exposure to EDCs leads to developmental cardiovascular adaptions and predisposes individuals to cardiovascular disease in later life.[6,7] This hypothesis is supported by previous studies showing that fetal exposure to bisphenols and phthalates is associated with often sex-specific cardiovascular risk factors, such as changes in blood pressure, low-grade albuminuria, and obesity in children.[8,9] Also, a recent study found that higher maternal urinary concentrations of phthalic acid, a derivate of most phthalates, in pregnancy were associated with a higher pericardial fat index in children age 10 y.[10] In adults, pericardial fat is associated with higher risks on cardiovascular disease.[11] Degenerative abnormalities of the vascular wall, such as atherosclerosis, are associated with an adverse cardiovascular status.[12] This process begins in childhood.[13–15] A few studies among adults and adolescents reported that higher urinary concentrations of bisphenols and phthalates were associated with the presence of clinical and subclinical atherosclerosis and arteriosclerosis.[16–19] To the best of our knowledge, no prior studies examined the associations of maternal bisphenol and phthalate exposure with arterial health in the offspring. Increased carotid intima-media thickness and decreased distensibility, which are assessed by ultrasonography, are well-accepted and commonly used markers of vascular wall properties and degeneration and independent predictors of future vascular events.[20–22] Also, in children, carotid intima-media thickness and distensibility are associated with cardiovascular risk factors such as hypercholesterolemia, obesity, and hypertension.[23] Detecting early risk factors for arterial damage enables intensified monitoring and preventive measures for future cardiovascular disease.

We hypothesized that fetal exposure to EDCs is associated with early markers of impaired arterial health from childhood onward. In a population-based prospective cohort study from early pregnancy onward among 935 mother–child pairs, we assessed the associations of maternal urinary bisphenol and phthalate concentrations during pregnancy with offspring carotid intima-media thickness and distensibility at the age of 10 y. We additionally explored whether any association varied according to child's sex or body mass index (BMI).[24,25]

Methods

Study Design

This study was embedded in the Generation R Study, a population-based prospective cohort study from fetal life until adulthood in Rotterdam, Netherlands. Study approval was obtained by the Medical Ethical Committee of the Erasmus Medical Center, University Medical Center, Rotterdam (MEC 198.782/2001/31).[26]

*Both authors contributed equally.
Address correspondence to Vincent W.V. Jaddoe, The Generation R Study Group (Na 29-15), Erasmus University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, Netherlands. Email: v.jaddoe@erasmusmc.nl

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Written informed consent was obtained from all mothers. The current study is an endocrine-disrupter subgroup study of the original cohort. Endocrine disrupters were assessed in a subgroup of 1,405 pregnant mothers with urine samples available, of whom 1,379 had urine samples at three time points in pregnancy. Of these, 935 mother–child pairs participated in follow-up studies of children at age 10 y. Other mother–child pairs were not eligible due to loss-to-follow-up (Flowchart shown in Figure 1).

Urinary Bisphenol and Phthalate Analysis

Maternal bisphenol and phthalate concentrations were measured in spot urine samples obtained from each woman at three time points during pregnancy [median 12.9 wk of gestation (95% confidence limit (CL): 9.8, 12.7 wk); median 20.4 wk of gestation (95% CL 18.9, 22.8 wk); median 30.2 wk of gestation (95% CL 28.8, 32.5 wk)]. Details of bisphenol, phthalate and creatinine measurements are reported elsewhere.[27] Analyses were performed at the Wadsworth Center, New York State Department of Health, Albany, New York, and at New York School of Medicine, New York, New York, by the same procedures and laboratory personnel.

Analytes were assessed individually and included when ≥20% of the samples showed values above the limit of detection (LOD) (Table S1). We selected the LOD cutoff of 20% because this cutoff enabled us to include the maximum number of participants in the analyses with adequate variability in the bisphenol data to detect associations. This approach is in line with previous studies in the field.[27–29] Statistical analysis were performed with concentrations of exposure expressed in nanomoles per liter. We grouped phthalates according to the molecular weight and parent phthalates into low-molecular-weight (LMW) phthalates and high-molecular-weight (HMW) phthalates. The LMW group in all three trimesters consisted of monomethyl phthalate, monoethyl phthalate, monoisobutyl phthalate, and mono-*n*-butyl phthalate. The HMW group in first trimester consisted of the di(2-ethylhexyl) phthalate group, the di-*n*-octyl phthalate group, monohexyl phthalate, mono-2-heptyl phthalate and monobenzyl phthalate. The HMW phthalate group in the second and third trimester consisted of the di(2-ethylhexyl) phthalate group, the di-*n*-octyl phthalate group and monobenzyl phthalate. The di(2-ethylhexyl) phthalate group in all three trimesters consisted of mono(2-ethyl-5-carboxypentyl) phthalate, mono (2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-oxohexyl) phthalate and mono[(2-carboxymethyl)-hexyl] phthalate. The di-*n*-octyl phthalate group in all three trimesters consisted of mono(3-carboxypropyl) phthalate. Phthalic acid was analyzed as a proxy for total phthalate exposure. We grouped individual bisphenols as a proxy for total bisphenol exposure. The total bisphenol group in first trimester consisted of bisphenol A, S, and F. The total bisphenol group in second trimester consisted of bisphenol A and S. The total bisphenol group in the third trimester consisted of bisphenol A and F. For bisphenol S and F, due to >80% of concentrations below LOD in one trimester, pregnancy-averaged concentrations were

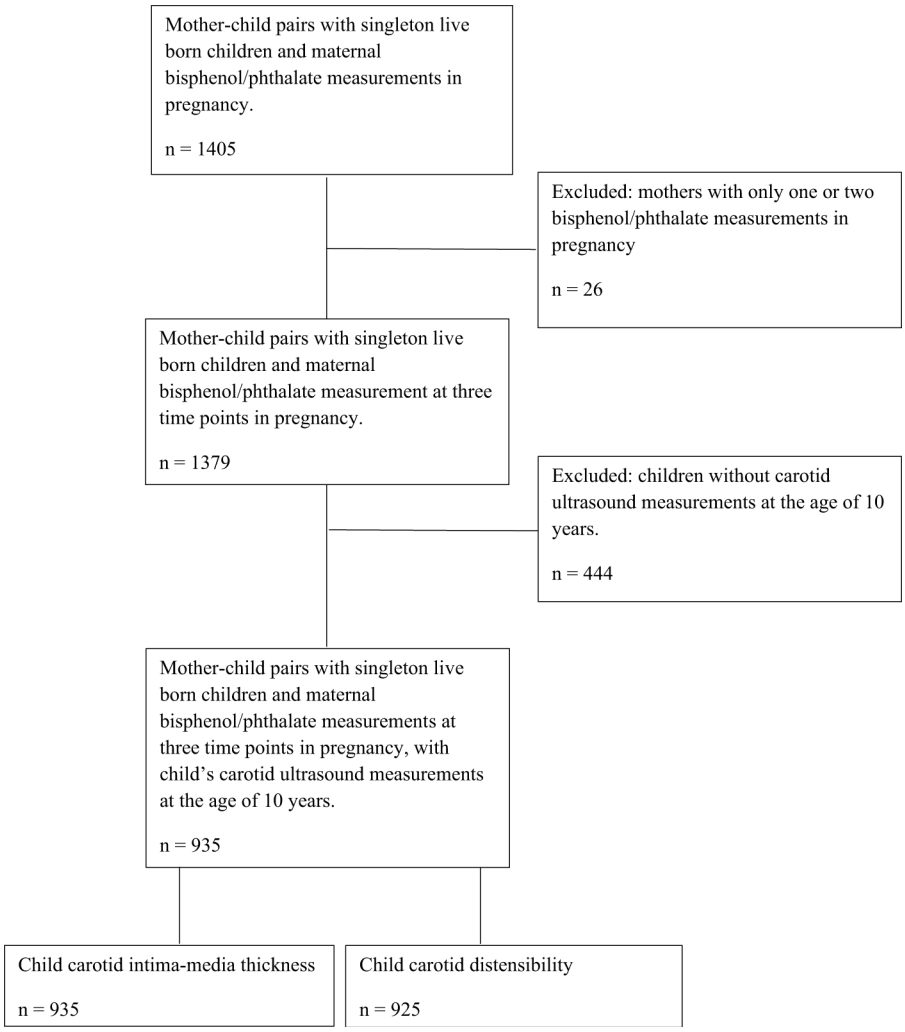

Figure 1. Flowchart of participants included in the study.

calculated based on urine concentrations measured in two trimesters. Grouping was performed by calculating the weighted molar sums of the individual metabolites for total bisphenol, LMW phthalate, HMW phthalate, di(2-ethylhexyl) phthalate, or di-*n*-octyl phthalate. Concentrations below the LOD were imputed by the LOD divided by the square root of 2, which has shown to provide an accurate estimation of the mean and standard deviation (SD) of exposure values in data that are not highly skewed.[30] We additionally measured child urinary bisphenol and phthalate concentration at age 6 y in a subgroup of 528 children using similar methods.[31]

Descriptive statistics of maternal individual and grouped bisphenols and phthalates are shown in Table S2. To account for urinary dilutions, we corrected for maternal urinary creatinine concentrations in micrograms per liter in all our models.[32] To reduce the potential for exposure misclassification due to temporal variability, we calculated the overall mean exposure during pregnancy. In addition, we explored trimester-specific effects. For all analyses, urine bisphenol and phthalate concentrations were natural log-transformed to reduce variability and account for right skewedness of the distribution and further standardized by the interquartile range to facilitate interpretation of the effect estimates.

Childhood Carotid Artery Intima-Media Thickness and Distensibility

Children were invited to the Erasmus University Medical Center at the median age of 9.7 y (95% CL: 9.2, 10.2 y) for ultrasonographic recordings of the common carotid arteries for carotid intima-media thickness and distensibility measurements using the Logiq E9 (GE Medical Systems). Within the Generation R study, a reproducibility study of 47 random subjects who were of the same age as those in our study sample, the subjects first underwent two ultrasounds at the same day by two different observers, followed by two ultrasounds a week later by the same observers. The interobserver and intraobserver intraclass correlation coefficients were both >0.85 for distensibility and 0.94 for intima-media thickness measurements. Children were in a supine position with their heads tilted in the contralateral direction. The common carotid artery was identified in a longitudinal plane ~ 10 mm proximal from the carotid bifurcation.[23] We obtained three recordings on both sides that included the coinciding cardiac cycles. Analyses were performed offline and semiautomatically using Carotid Studio (Cardiovascular Suite; Quipu srl).[20] The recording was frozen on each R-wave of the simultaneous electrocardiogram; the carotid intima-media thickness was then measured at the far wall as the average distance between lumen-intima and media-adventitia border.[33] The average carotid intima-media thickness of all frames was computed. Carotid distensibility was defined as the relative change in lumen area during systole for a given pressure change. Lumen diameter was automatically computed as the average distance between the far and near media-adventitia interfaces for each frame of the acquired image sequence. Distension was calculated as the difference between the diastolic and systolic lumen diameter for each cardiac cycle in the recording.[34] The average distension and diameter measurements were used to compute distensibility. We included all children with at least one successful carotid intima-media thickness or distensibility measurement, and the mean values were used for further analysis. The overall mean carotid intima-media thickness (millimeters) and distensibility (per kilopascal $\times 10^{-3}$) were used as main outcomes of interest. For analyses, distensibility was log-transformed to obtain normal distributions, and carotid intima-media thickness and distensibility were SD score transformed.

Covariates

Information on maternal educational level (completed primary school, secondary school, or higher), parity (nulliparous or multiparous), prepregnancy weight, folic acid supplementation use (yes or no), alcohol use (never, until pregnancy was known, or continued in pregnancy) and smoking (never, until pregnancy was known, or continued in pregnancy) was obtained through questionnaires. Information on maternal ethnicity was obtained from questionnaires, and women were categorized in the groups as Dutch, European, or non-European (including Indonesian, Cape Verdean, Moroccan, Surinamese, Turkish, African, American, Asian, and Oceanian women). To obtain information on maternal kilocalorie intake, nutritional intake in the prior 3 months was assessed in early pregnancy using a modified version of a validated semiquantitative food frequency questionnaire.[35] Maternal height was measured at time of enrollment without shoes and prepregnancy BMI was calculated.[26] We obtained information about child's birth weight, gestational age at birth, and sex from medical records. In children age 10 y, weight and height were measured without shoes, and BMI was calculated. We calculated child's age adjusted BMI.[36]

Statistical Analysis

First, to identify potential nonresponse bias, we compared the characteristics of the mother–child pairs with and without child carotid ultrasonography at the age of 10 y among those with maternal urinary bisphenol and phthalate measurements in pregnancy. We used chi-square test, Student's *t*-test, and Mann-Whitney U tests when applicable. Second, we explored the correlation structure of the data by calculating pairwise Pearson's correlation coefficients between the exposure groups, within each trimester, on average and between trimesters. Correlations of 0–0.29, 0.3–0.49, 0.5–0.69, 0.7–0.89, and 0.9–1.0 were considered to be very low, low, moderate, high, and very high, respectively.[37] We visualized these correlations using heat maps (R package ggplot2). Additionally, we explored the correlation of maternal average urinary concentrations of the main exposure groups with child urinary concentrations of these exposures at age 6 y to assess whether the exposures were potential confounders via household level consumption patterns. Third, we examined the associations of average and trimester-specific maternal urinary total bisphenol; bisphenol A, S, and F; phthalic acid; LMW phthalate; HMW phthalate; di(2-ethylhexyl) phthalate; and di-*n*-octyl phthalate concentrations with the mean of all carotid intima-media thickness measurements and mean of all carotid distensibility measurements in children using linear regression models.

Analyses were first only adjusted for child's sex and age and maternal urinary creatinine concentrations in the basic model; analyses were subsequently adjusted for maternal sociodemographic and lifestyle factors in the adjusted model. Confounders were selected from previous literature and were defined using a Direct Acyclic Graph (Figure S1). Maternal potential confounders were age, parity, prepregnancy BMI, educational level, alcohol use, smoking, kilocalorie intake as proxy for maternal diet, and folic acid supplementation.[27,38–43] Of these, we included the confounders in the adjusted models that changed the effect estimated for $>10\%$ for at least one outcome; based on these criteria, we excluded maternal kilocalorie intake. We considered this adjusted model to be the main model. We additionally applied an inverse probability of treatment weighted analysis for the analysis of the average exposures, because this method has been shown to lead to more robust and less biased estimations of the effect with many potential confounders.[44] We used linear regression propensity score models to calculate weights for each exposure group (R

package ipw). The use of these weights allowed us to estimate the average exposure effect. The underlying propensity score models included maternal age, parity, prepregnancy BMI, educational level, alcohol use, smoking, kilocalorie intake, folic acid supplementation, child age, and child sex.[27,38–43] We checked for weight model misspecifications by exploring the distribution of the weights. Weights were truncated at the first and 99th percentile.[45]

Because we hypothesized sex-specific effects based on previous literature[28] and a different hormonal physiology in boys and girls, we tested for statistical interaction of child's sex for each exposure, considering a p-value threshold of <0.10. Also, based on previous studies suggesting an association of higher exposure to bisphenol and phthalates and childhood obesity, we considered child BMI a potential mediator.[46,47] Therefore, we performed a mediation analysis on child's age-adjusted BMI (R package: mediation).[48] We assessed the average causal mediation effects, the average direct effects, and the proportion mediated. We obtained the confidence intervals of the causal mediation effects using bootstrapping with 1,000 resamplings. Because the associations of the main analysis might differ among ethnic subgroups, we performed a sensitivity analysis including only Dutch mothers, which was the largest ethnicity group. Next, we performed a sensitivity analysis, including only bisphenols and phthalates with >50% of values above the LOD. We did this to explore whether a lower variability due to replacement of a large number of values below the LOD reduced the ability to detect associations. Then, we performed an analysis including similar bisphenols and phthalates in grouping in all three trimesters, regardless of the percentage of values below LOD, to ensure that the differences in grouping across trimesters did not bias our estimates. For this, we took the exposures included in first trimester grouping in the main analysis as reference. Last, to assess the effect of nonresponse on the estimates, we performed a sensitivity analysis, adding inverse probability of censoring weights to the main analysis. We used logistic regression propensity score models to calculate weights for response or nonresponse. The underlying propensity score models included baseline characteristics potentially related to nonresponse, being maternal age, parity, prepregnancy BMI, educational level, alcohol use, and smoking. We checked for weight model misspecifications by exploring the distribution of the weights.

Missing values were imputed using multiple imputation by the fully conditional specification method, which creates imputations per variables in an iterative fashion based on an imputation model for each incomplete variable.[49] Pooled results from five imputed data sets were reported. The percentage of missing values for covariates ranged from 0% to 5%, except for folic acid supplementation (20% missing values). Maternal urinary bisphenol A and phthalic acid concentrations and child mean carotid intima-media thickness and distensibility were included as predictors for the imputation of covariates. All statistical tests were 2-sided and p-values for all analysis were presented. To correct for multiple hypothesis testing, each p-value was compared with a threshold defined as 0.05 divided by the effective number of independent tests estimated based on the correlation structure between the exposures ($p = 0.0098$).[28,50] The analyses were performed using the Statistical Package for the Social Sciences (SPSS; version 25.0; IBM Corp.) and R Statistical Software (version 4.1.0; R Development Core Team).

Results

Subject Characteristics

At enrollment, the mean maternal age was 30.9 y (SD ± 4.6 y), the median BMI was 22.6 kg/m^2 (IQR: 20.9, 25.2 kg/m^2), and most women were Dutch, nulliparous, and highly educated (Table 1).

Table 1. Characteristics of the study population, consisting of 935 Dutch mothers, included in pregnancy between 2002 and 2006, and their children. Mothers are measured in pregnancy, and children at age 10 y.

Characteristics	Total sample $n = 935$
Maternal characteristics	
Maternal age in years [mean (±SD)]	30.89 (4.59)
Ethnicity [n (%)]	
Dutch	538 (57.8)
European	79 (8.5)
Non-European	314 (33.7)
Parity [n (%)]	
Nullipara	583 (62.4)
Multipara	352 (37.6)
Prepregnancy BMI [kg/m^2, median (IQR)]	22.60 (20.89, 25.18)
Folic acid supplementation in pregnancy [n (%)]	
Yes	623 (83.5)
No	123 (16.5)
Smoking [n (%)]	
Never smoked during pregnancy	651 (77.0)
Smoked until pregnancy was known	80 (9.5)
Continued smoking in pregnancy	115 (13.6)
Alcohol use [n (%)]	
Never alcohol in pregnancy	318 (37.8)
Alcohol until pregnancy was known	161 (19.1)
Alcohol continued in pregnancy	362 (43.0)
Highest education completed [n (%)]	
No education	1 (0.1)
Primary	58 (6.4)
Secondary	361 (39.8)
Higher	486 (53.6)
Child characteristics	
Sex [n (%)]	
Male	480 (51.3)
Female	455 (48.7)
Age of child at visit in years [mean (±SD)]	9.67 (0.22)
BMI [kg/m^2, median (IQR)]	16.79 (15.53, 18.38)
Mean carotid intima-media thickness in millimeters [mean (SD)][a]	0.45 (0.05)
Mean carotid distensibility [per kilopascal $\times 10^{-3}$ median (IQR)][a]	55.80 (48.78, 64.83)

Note: Values presented as mean (±SD), median (IQR), or number of participants (valid percent). Number of missing per covariate: maternal ethnicity, $n = 4$(0.4%); prepregnancy BMI, $n = 108$(11.5%); folic acid supplementation, $n = 189$(20.2%); smoking, $n = 89$(9.5%); alcohol use, $n = 94$(10.1%); education, $n = 29$(3.1%); child BMI, $n = 2$(0.2%); carotid distensibility, $n = 10$(1.1%). BMI, body mass index; IQR, interquartile range; SD, standard deviation.
[a]Mean of all measurements of the left and right carotid arteries.

Most women had never smoked but continued consuming alcohol in pregnancy. The mean age of children when the carotid ultrasound was performed was 9.7 y (SD ± 0.2 y), and median BMI was 16.8 kg/m^2 (IQR: 15.5, 18.4 kg/m^2). The mean carotid intima-media thickness of our study sample was 0.45 mm (SD ± 0.05 mm), and the mean distensibility was 55.80 $kPa^{-1} \times 10^{-3}$ (IQR: 48.78, 64.83 $kPa^{-1} \times 10^{-3}$). Nonresponse analysis showed that in all mother–child pairs with maternal urinary bisphenol and phthalate measurements in pregnancy, mothers in our study were slightly older, were more often Dutch, and consumed alcohol in pregnancy more often, in comparison with mother–child pairs without child carotid ultrasound at the age of 10 y (Table S3).

Correlation Structure

Figure 2 shows the correlation of the average exposure groups. Correlations were very low or low among all exposure groups, except for the correlations between HMW phthalate and di(2-ethylhexyl) phthalate (Pearson's correlation 1.0) and between total bisphenol and bisphenol A (Pearson's correlation 0.98). Figure S2 shows the correlations of the exposure groups in each trimester and between trimesters. Within trimesters, correlations were very low or low, except for the

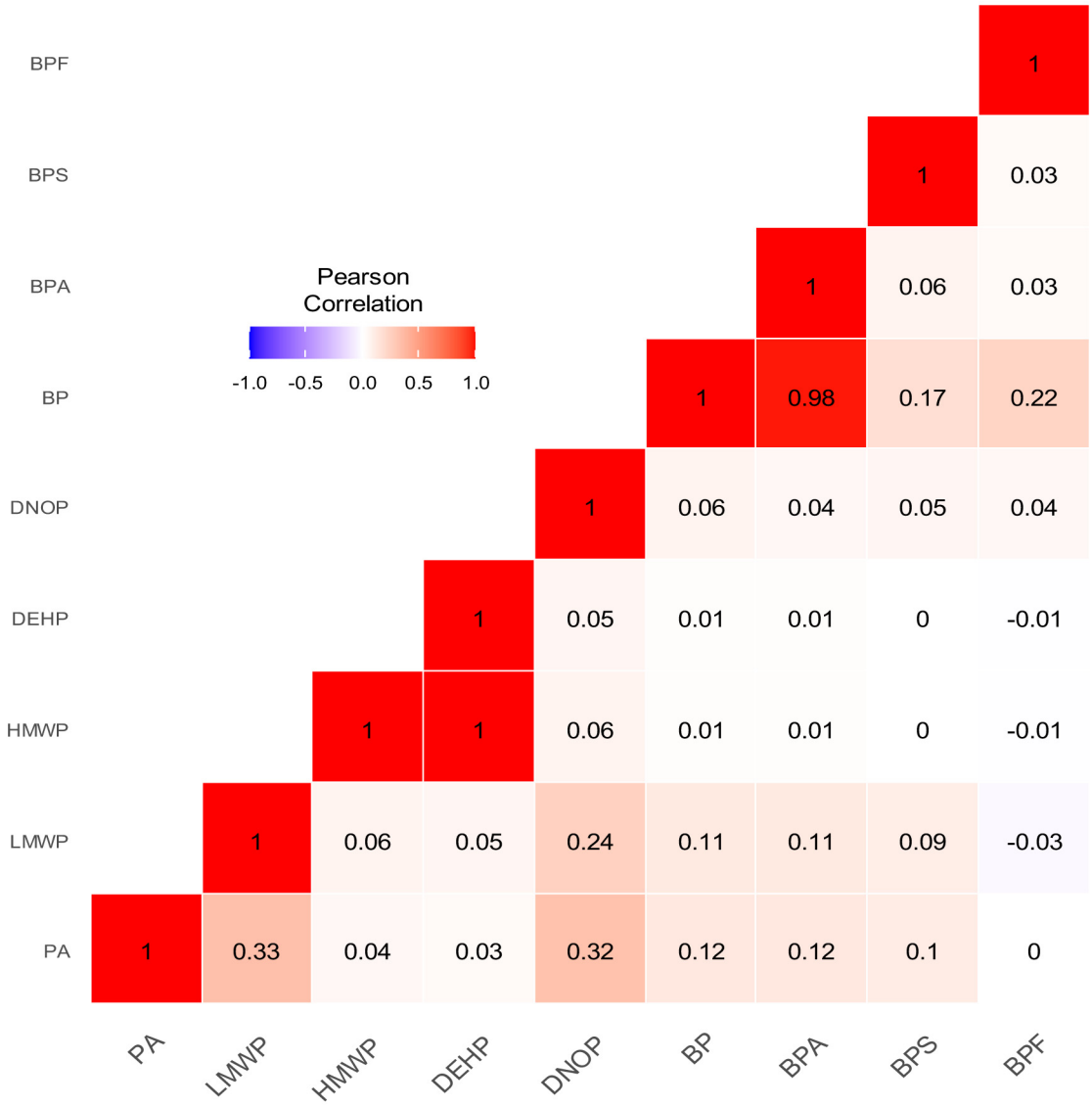

Figure 2. Heat map on the correlation between average exposure groups. Values represent Pearson's correlation coefficient on the correlation between the average maternal urinary exposure groups. Note: BP, total bisphenol; BPA, bisphenol A; BPF, bisphenol F; BPS, bisphenol S; DEHP, di-2-ethylhexylphthalate; DNOP, di-*n*-octyl phthalate; HMWP, high-molecular-weight phthalate; LMWP, low-molecular-weight phthalate; PA, phthalic acid.

high correlations of HMW phthalate with di(2-ethylhexyl) phthalate and of total bisphenol with bisphenol A within the first and third trimester and the moderate correlations of second trimester LMW phthalate with di-*n*-octyl phthalate and of third trimester phthalic acid with LMW phthalate. Between trimesters, all correlations were low or very low. Figure S3 shows that the correlation between maternal average urinary concentrations and child urinary concentrations at age 6 was very low for all main exposure groups. Therefore, we did not adjust for child bisphenol and phthalate concentrations in further analyses.

Carotid Intima-Media Thickness

Average maternal phthalic acid, LMW HMW phthalate, di(2-ethylhexyl) phthalate and di-*n*-octyl phthalate concentrations were not associated with child carotid intima-media thickness at age 10 y (Figure 3; see also Table S4). After we accounted for multiple testing, higher average maternal urinary concentrations of total bisphenol, and especially bisphenol A, were associated with a lower carotid intima-media thickness (differences −0.15 SD score (95% CI: −0.24, −0.06) per IQR increase in total bisphenol concentration and −0.13 (−0.22, −0.04) per IQR increase in bisphenol A concentration). Trimester-specific analysis showed associations of higher third trimester maternal total bisphenol and bisphenol A concentrations with lower carotid intima-media thickness (Table S5). The analysis of the basic model and of the model using inverse probability of treatment weighting yielded effects estimates largely similar to those of the main model (Tables S4 and S5).

Carotid Distensibility

Average and trimester-specific maternal urinary bisphenol or phthalate concentrations were not associated with child carotid distensibility at age 10 y (Figure 4; see also Table S6 and S7).

Sensitivity Analyses

We tested for statistical interaction of child's sex. Only the interaction term of HMW phthalate and sex reached a $p < 0.10$ in the association of average maternal urinary exposure and child

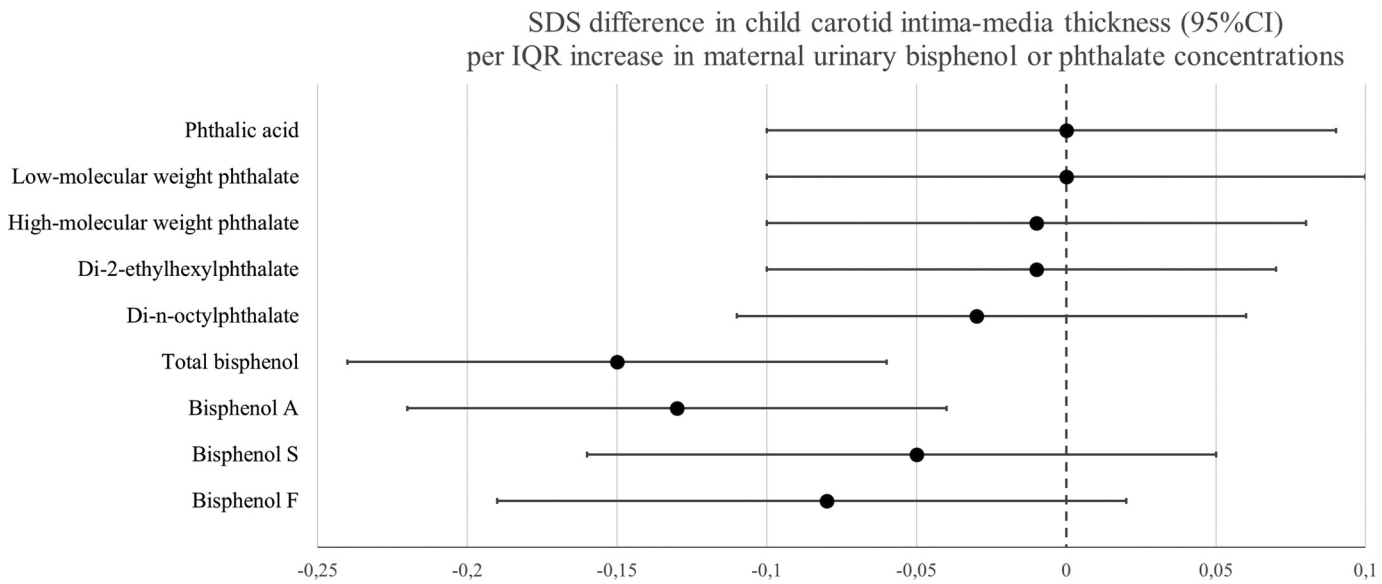

Figure 3. Associations of average maternal bisphenol and phthalate urine concentrations in pregnancy with child carotid intima-media thickness at age 10 y. Values represent regression coefficients (95% CI) of the regression models that reflect the difference in SDS of child's carotid intima-media thickness (in millimeters) for an IQR increase in maternal urinary phthalate and bisphenol (nanomoles per liter). Model is corrected for maternal age, parity, prepregnancy BMI, educational level, smoking and alcohol use, child's age and gender, and maternal urinary creatinine. Corresponding numeric data are reported in Table S4. Note: CI, confidence interval; IQR, interquartile range; SDS, standard deviation score.

carotid distensibility at age 10 y (Table S8 and S9). Therefore, we performed no analysis stratified on child's sex. Our mediation analysis showed that child's age-adjusted BMI at age 9 y did not mediate any association and did not change the effect estimates of the associations when added as confounder to the main model (Table S10 and S11). Also, analysis including only Dutch mother–child pairs yielded similar effects in comparison with the whole group (Table S12 and S13). We performed a sensitivity analysis that included only bisphenols and phthalates with >50% of values above the LOD. With these criteria, the groupings changed to HMW phthalate and di(2-ethylhexyl) phthalate, excluding first trimester monocyclohexyl phthalate, and to total bisphenol, excluding first and third trimester bisphenol F and second trimester bisphenol S (Table S1). The analysis that included only exposures with >50% of values above LOD yielded effects similar to those found in the analysis that included exposures with >20% of values above the LOD (Table S14 and S15). Similarly, sensitivity analysis including the same exposures in grouping in all three trimesters yielded effects similar to those found in the main analysis (Table S16 and S17). Last, the analysis that included inverse probability of censoring weights did not significantly change our effect estimates (Table S18 and S19).

Discussion

Results from this population-based prospective cohort study suggest that higher average and third-trimester maternal urinary total bisphenol and bisphenol A concentrations are associated with a lower carotid intima-media thickness in children age 10 y. Maternal phthalate concentrations were not associated with child carotid intima-media thickness. Neither maternal bisphenols, nor maternal phthalate concentrations were associated with carotid distensibility.

Interpretation of Main Findings

EDCs such as bisphenols and phthalates are among the most widely used chemical compounds in the production of common consumer products worldwide.[1–4] Although some bisphenols and phthalates such as bisphenol A are being regulated, their global production is still substantial, and the production of substitutes such as bisphenol S and F is rising.[51] Fetal exposure to bisphenols and phthalates might cause developmental cardiovascular adaptations by influencing fetal vascular development.[5–7,52]

Based on studies among adults, we hypothesized that higher maternal urinary concentrations of bisphenols and phthalates are associated with the development of early markers of impaired arterial health.[16–18] In contrast with our hypothesis, we observed associations of higher maternal urinary total bisphenol, and specifically bisphenol A concentrations, with lower carotid intima-media thickness. These unexpected associations were observed in the basic and fully adjusted model, corrected for maternal or child sociodemographic or lifestyle factors. To the best of our knowledge, no previous studies have been published on the association of maternal bisphenol exposure with markers of arteriosclerosis in the offspring. A few previous studies in adults suggested that higher exposure to bisphenol A and several phthalates was associated with a higher carotid intima-media thickness and higher echogenicity of the vascular wall and carotid plaques.[17–19] The discrepancy of results between our study and those reported earlier may be explained by different pathophysiological mechanisms. In adults the association between higher bisphenol A and atherosclerosis was explained by increased oxidative stress in the vascular wall and through mediation with cardiovascular risk factors.[17,18] Oxidative stress might accelerate the formation of atherosclerotic plaques in the vascular wall. However, in fetuses, higher exposure to bisphenols might interfere with cardiovascular development, causing structural adaptations in the vascular wall rather than the development of carotid plaques. In general, a thicker carotid intima-media in children is associated with an adverse cardiovascular risk profile, such as obesity, hypertension, and hypercholesterolemia. However, associations of carotid intima-media thickness in childhood with vascular health in later life have not yet been investigated.[23] A thinner carotid intima-media might represent underdevelopment of the vasculature. This underdevelopment might contribute to an endothelium that is more vulnerable for exposures in later life, which could explain a

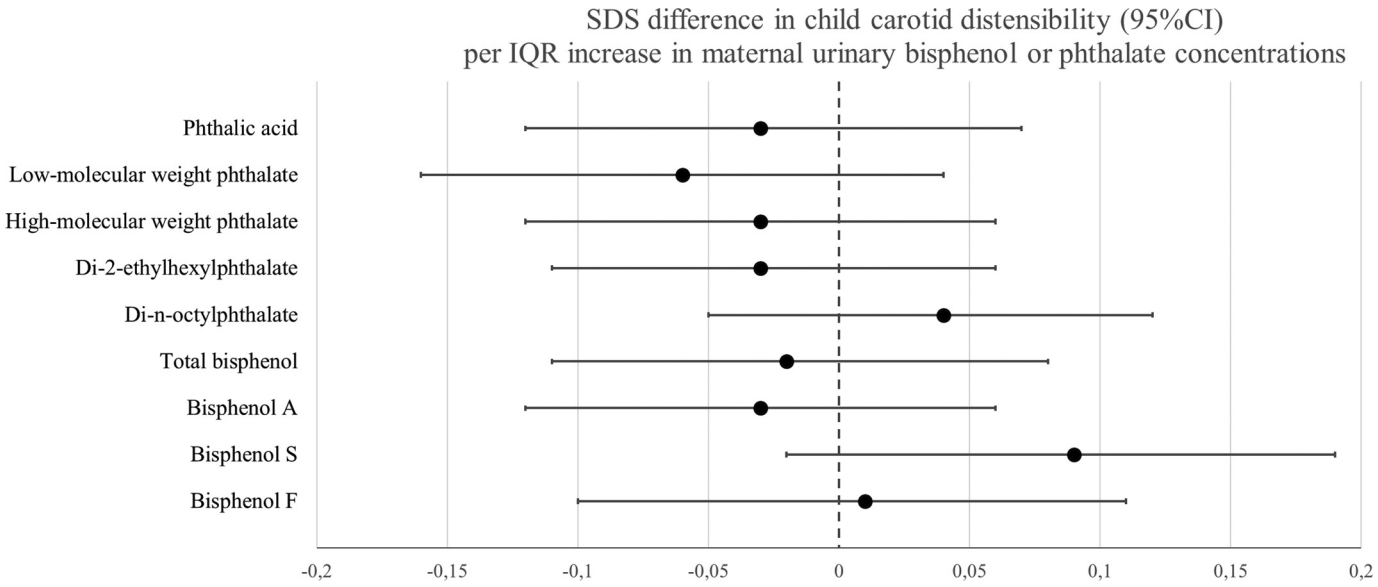

Figure 4. Associations of average maternal bisphenol and phthalate urine concentrations in pregnancy with child carotid distensibility at age 10 y. Values represent regression coefficients (95% CI) of the regression models that reflect the difference in SDS in natural log-transformed carotid distensibility (in $kPa - 1 \times 10^{-3}$) for an IQR increase in maternal urinary phthalate and bisphenol (nanomoles per liter). Model is corrected for maternal age, parity, ethnicity, prepregnancy BMI, educational level, smoking and alcohol use, child's age and gender, and maternal urinary creatinine. Corresponding numeric data are reported in Table S6. Note: BMI, body mass index; CI, confidence interval; IQR, interquartile range; SDS, standard deviation score.

reversal of the association in adulthood. Although differences were small and without clear individual-level impact, our results are important from a population perspective, because they show the potential influence of exposure to EDCs on fetal cardiovascular development.

Bisphenols are weak xenoestrogens with binding affinity to, among others, the estrogen receptors α and β, and both receptors have been shown to attenuate injury-induced vascular remodeling.[8,53] Also, studies suggest that bisphenol A is equally as potent as estradiol and increases 17β-estradiol levels, and bisphenol F appears to be even more potent.[8] It is interesting to note that 17β-estradiol has vasoprotective and anti-inflammatory capacities.[53] Therefore, the increase of 17β-estradiol induced by bisphenols might influence fetal vascular development. Another mechanism through which higher exposure to bisphenols might alter vascular development is by activating peroxisome proliferator–activated receptor γ (PPARγ), which mainly expresses in adipose tissue and regulates adipogenesis, lipid storage, and glucose homeostasis.[54,55] Accumulating evidence demonstrates that PPARγ agonists have potential for treatment of atherosclerosis to improve the endothelial function, slow down the progression of atherosclerotic plaques, and reduce chronic inflammation and thrombosis.[55]

Our results should be interpreted with caution. First, fetal vascular development is highly dependent on a wide variety of genetic and lifestyle factors. Second, other adverse offspring cardiometabolic effects of exposure to maternal bisphenol concentrations should be taken into account. For example, higher maternal urinary bisphenol A concentrations have been associated with both lower and higher childhood BMI, waist circumference, and blood pressure, and with increased low-grade albuminuria, whereas no studies have been performed on the substitutes bisphenol S and F.[8,28] Third, especially in children, physiological remodeling of the medial layer in response to physiological developmental changes in body dimension and blood pressure may be an additional or alternative explanation for changes in the intima-media thickness.[56] Associations were mainly present in the third trimester, possibly because in the first trimester fetuses are not yet fully exposed to bisphenols because the placenta is still under development, and in second trimester maternal and subsequently fetal concentrations of bisphenols were lower due to the physiological increase in maternal serum in this phase of pregnancy.

Methodological Considerations

This analysis benefited from the large population, the prospective data collection from early pregnancy onward, and the availability of a wide range of covariates. Also, phthalates and bisphenols, including uncommon substitutes for common microplastics, were measured repeatedly throughout pregnancy. Our population concerned a relatively highly educated population in comparison with the full cohort, and women in our sample were more often Dutch and used alcohol more often, as is shown in our nonresponse analysis. This particular population might have affected the generalizability of our results. However, our sensitivity analysis including inverse probability of censoring weights yielded effects similar to those of the main analysis, indicating minimal nonresponse bias. Urinary concentrations of bisphenol and phthalates were measured only once per trimester. However, previous studies have shown that urinary phthalate and bisphenol measurement might reasonably reflect exposures in the prior several weeks or even months.[8] Bisphenol and phthalate concentrations in urine were lower in second trimester in comparison with the first and third trimesters. We hypothesized that this was caused by physiological serum dilution in second trimester of pregnancy. Differences in exposure concentration in urine might also be due to differences in the time of day of sampling.[39] We replaced phthalate and bisphenol concentrations below LOD with the LOD divided by the square root of 2. Overall, the percentages of metabolites below LOD were reasonable (<35%), except for bisphenol F (on average 65.3% below LOD). This might have reduced variability in the exposure and therefore the ability to detect associations We did not include the same metabolites in the exposure groups in each trimester. However, we expect that the contributions of the chemicals that were not included due to a high percentage of values below the LOD is negligible, because most values that were excluded would be imputed and would not contribute to the variability of the exposure. This

consideration was supported by our sensitivity analysis including the same exposures in groupings across trimesters. As for the outcome, although we demonstrated high reproducibility, we cannot exclude observer bias in the carotid measurements. Last, although we corrected for many potential confounders, residual confounding due to the observational nature of the study might have occurred.

Summary and Implications

To our best knowledge, this study is the first study assessing the association of maternal urinary bisphenol and phthalate concentrations with childhood carotid intima-media thickness and distensibility. We observed that higher average and third-trimester maternal urinary total bisphenol and bisphenol A concentrations were associated with smaller childhood carotid intima-media thickness. Additional large prospective cohort studies are needed to get better understanding of the pathophysiological mechanisms underlying the effects of EDCs on vascular development, possibly including measurements of steroids, markers of oxidative stress, or even metabolomics analysis to assess more fundamental changes in metabolism.

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